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Archival Report

Early-Life Critical Windows of Susceptibility to Manganese Exposure and Sex-Specific Changes in Brain Connectivity in Late Adolescence

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ABSTRACT

BACKGROUND: Early-life environmental exposures during critical windows (CWs) of development can impact life course health. Exposure to neuroactive metals such as manganese (Mn) during prenatal and early postnatal CWs may disrupt typical brain development, leading to persistent behavioral changes. Males and females may be differentially vulnerable to Mn, presenting distinctive CWs to Mn exposure.

METHODS: We used magnetic resonance imaging to investigate sex-specific associations between early-life Mn uptake and intrinsic functional connectivity in adolescence. A total of 71 participants (15–23 years old; 53% female) from the Public Health Impact of Manganese Exposure study completed a resting-state functional magnetic resonance imaging scan. We estimated dentine Mn concentrations at prenatal, postnatal, and early childhood periods using laser ablation–inductively coupled plasma–mass spectrometry. We performed seed-based correlation analyses to investigate the moderating effect of sex on the associations between Mn and intrinsic functional connectivity adjusting for age and socioeconomic status.

RESULTS: We identified significant sex-specific associations between dentine Mn at all time points and intrinsic functional connectivity in brain regions involved in cognitive and motor function: 1) prenatal: dorsal striatum, occipital/frontal lobes, and middle frontal gyrus; 2) postnatal: right putamen and cerebellum; and 3) early childhood: putamen and occipital, frontal, and temporal lobes. Network associations differed depending on exposure timing, suggesting that different brain networks may present distinctive CWs to Mn.

CONCLUSIONS: These findings suggest that the developing brain is vulnerable to Mn exposure, with effects lasting through late adolescence, and that females and males are not equally vulnerable to these effects. Future studies should investigate cognitive and motor outcomes related to these associations.

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The Developmental Origins of Health and Disease theory postulates that early-life environmental influences can result in long-lasting effects on health (1). Indeed, exposure to toxicants during critical windows (CWs) of development has been shown to alter tissue-specific plasticity by interfering with maturational processes, leading to functional changes in various organ systems throughout the life course (2). Such CWs result from gene-environment interactions, giving rise to sensitive periods during development in which the formation of a phenotype is responsive to external factors (3). These changes may increase susceptibility to disease and dysfunction later in life (4,5). This reprogramming process depends on 1) the sensitivity of a specific tissue to the chemical and 2) a temporal overlap between exposure and the tissue's CW of development. In addition, the time window in which the phenotype/outcome is measured plays an important role in estimating the impact of exposure (1,6). The extended period of brain development, spanning the third gestational week through late adolescence, gives rise to many CWs of vulnerability to toxic chemicals across development (e.g., prenatal, early postnatal, and childhood periods) (7). Extensive evidence suggests that the effects of environmental exposure on neurodevelopment may depend as much on the exposure timing as on the concentration (8,9). A better understanding of CWs of vulnerability to developmental neurotoxicants and the biological mechanisms underlying these associations would inform our understanding of typically developmental trajectories as well as inform prevention and treatment strategies for reducing adverse environmentally associated brain outcomes.

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Magnetic resonance imaging (MRI) provides insight into biological mechanisms underlying human cognition and behavior. Applied to studies of environmental epidemiology, MRI offers the possibility of linking exposure with changes in the brain. Specifically, resting-state functional MRI (rs-fMRI) can be used to map large-scale functional networks in the human brain by examining slow (<1 Hz) oscillatory intrinsic fluctuations in hemodynamics (10), with the assumption that regions with correlated activity form functional networks. Changes in brain functional connectivity have been reported in various neurodevelopmental disorders (11). rs-fMRI is particularly suited to benefit pediatric research because it is inherently noninvasive and does not require cooperation or motivation, minimizing many confounders related to task performance and increasing consistency across participants and datasets (12). Incorporating rs-fMRI into children's environmental health studies allows us to examine the in vivo impacts of environmental exposures on the developing brain's functional organization (13).

Throughout development, the brain undergoes a complex series of dynamic processes in which few cells develop into a highly interconnected brain (7,14). Environmental exposure to neuroactive metals such as manganese (Mn) during specific CWs of brain development may disrupt typical development and functioning, leading to persistent behavioral and cognitive changes (14,15). The general population can be exposed to Mn through inhalation, dietary intake, and drinking of contaminated water (16–18). Human activities such as ferroalloy industries may expose children and pregnant women residing in adjacent areas to higher levels of Mn (19). Mn can cross the placental and blood-brain barriers and lead to changes in the brain (20). Mn levels outside of the homeostatic range (i.e., deficiency or intoxication) alter neuron function (21,22), increase oxidative stress (23), accumulate in the basal ganglia (21–23), and adversely affect cognitive and behavioral outcomes including IQ (24,25), motor function (19,26,27), and hyperactivity (28,29). While CWs to Mn have been identified during gestation, infancy, early childhood, and adolescence (8,9,30,31), the brain mechanism underlying its neurotoxicity remains largely unknown. Further, animal and human studies demonstrate sex-specific associations between Mn exposure and behavioral outcomes (26,32–34), suggesting that males and females may present distinctive CWs to Mn exposure and may be differentially vulnerable to its effects. Sex-specific vulnerability may relate to the brain's sexually dimorphic developmental trajectory, beginning in utero (35–37). Sex differences in developmental trajectories may emerge from endogenous developmental programming, developmental experience, or other environmental exposures (38–40). Sex-specific CWs may explain sex differences in the prevalence, severity, and progression of neurodevelopmental disorders. Understanding the impact of both timing and concentration of Mn exposure on brain functional connectivity may provide mechanistic insights into sex differences in Mn-associated neurotoxicity.

In this study, we used rs-fMRI to investigate sex-specific associations between prenatal, early postnatal, and childhood Mn exposure, measured in deciduous teeth, and brain intrinsic functional connectivity (iFC) in older adolescents. Notably, sex differences in associations between Mn and neurocognition have been previously reported in this cohort (32,41). Based on previous studies suggesting associations between early-life Mn exposure and changes in brain areas implicated in motor and cognitive control (42–46), we hypothesized that early-life exposure to Mn will have downstream impacts on brain functional connectivity in the basal ganglia, prefrontal cortex, parietal cortex, and motor cortex and that these effects will be different in females compared with males.

METHODS AND MATERIALS

Participants

Participants were part of the ongoing Public Health Impact of Metal Exposure (PHIME) cohort based in the province of Brescia in Northern Italy. Details of the study recruitment and enrollment have been described previously (19). Briefly, participants were enrolled in the study using a community-based participatory approach from schools throughout the local public school system in Northern Italy. Schools are located in 3 geographically different but demographically similar communities in the province of Brescia, characterized by the presence of ferroalloy plants causing Mn exposure through airborne emission. All participants completed baseline questionnaires to evaluate inclusion and exclusion criteria. Inclusion criteria included birth in the study area of interest, residence in the study area since birth, and family residence in the study area since the 1970s. Exclusion criteria included known neurologic, hepatic, metabolic, endocrine, or major psychiatric disorder; medication usage with known neuropsychological side effects; clinically diagnosed motor deficits or cognitive impairment; and visual deficits that are not adequately corrected. A total of 720 adolescents were enrolled in the Public Health Impact of Metal Exposure cohort between 2007 and 2014. At the time of enrollment, participants were asked to provide a naturally shed deciduous tooth. Between 2015 and 2020, 207 subjects (age 16–23 years) participated in a multimodal MRI follow-up study and completed baseline questionnaires, including information on parental educational and occupational levels, and neuropsychological tests, including IQ using the Wechsler Intelligence Scale for Children-III assessment (47). Between 2015 and 2016, a convenience sample of teeth from 195 (27%) participants were analyzed for early-life Mn. From this sample, MRI scans were acquired for 73 subjects. Complete exposure data (i.e., dentine Mn), outcome (MRI data), and covariate data were available for the 73 adolescents (38 females) included in this analysis. After excluding 2 participants due to movement in the scanner, Mn uptake, MRI scans, and covariate data were available for 71 adolescents (38 females). This study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai and the Public Health Agency of Brescia. Written informed consent was obtained from all participants.

Dentine Mn Biomarker

To identify early-life CWs of vulnerability to Mn, we used deciduous teeth as a biomarker of retrospective exposure. Because deciduous teeth accumulate metals in a pattern similar to the growth rings of a tree, they can provide estimates

of both the timing and intensity of exposure, allowing us to detect when exposure is most hazardous (48). Only incisors, canines, and molars that were free of defects such as caries and extensive tooth wear, were analyzed. Detailed analytic methods have been described previously (48–50). Briefly, teeth were washed in an ultrasonic bath of ultrapure Milli-Q water (18.2 MΩ/cm) and sectioned on a vertical, labial-lingual, or buccal-lingual plane using a diamond-encrusted blade. The neonatal line, which histologically distinguishes pre- and postnatally formed regions of dentine, was identified using light microscopy. With the neonatal line as a reference point, the concentrations and spatial distribution of Mn in different developmental windows were determined using laser ablation–inductively coupled plasma–mass spectrometry. Dentine Mn concentrations were normalized to dentine calcium levels (^{55}Mn:^{43}Ca ratio) to account for variations in mineral density within and between teeth. A total of 30 sampling points were ablated parallel to the enamel-dentine junction and assigned to pre- or postnatal zones after identifying the neonatal line. Area under the curve was used to account for the different number of sampling points in each zone per tooth. Childhood cumulative Mn concentrations (1 to ~6 years of age) were determined by averaging across 10 sampling locations within secondary dentine, the formation of which starts after the completion of the tooth root and proceeds at a slower rate. The limit of detection was 0.02 μg/g. Only one dentine measurement fell below the detection limit (n = 1) and was assigned half the lowest value among the samples above the detection limit.

Covariates

Given that age and socioeconomic status (SES) may impact iFC (51,52) and associations between Mn exposure and neurodevelopment (53), we included these variables as covariates in the analyses. SES index (low, medium, high) was determined using parental educational and occupational levels (54).

MRI Data Acquisition

The MRI scan was performed on a 3T MR unit (Skyra, Siemens) equipped with a 64-channel phased array head coil at the Neuroimaging Division at the ASST Spedali Civili Hospital of Brescia. The 10-minute rs-fMRI scans were acquired using a T2*-weighted echo-planar imaging sequence (repetition time = 1000 ms, echo time = 27 ms, 70 axial slices, 2.1-mm thickness, matrix size 108 × 108, covering the brain from vertex to cerebellum). During this acquisition, lights were turned off and subjects were instructed to keep their eyes open and stare at a night skyline picture projected on the monitor, to not think of anything specific, and to not fall asleep. For registration purposes, we acquired a high-resolution anatomical T1-weighted scan using three-dimensional magnetization-prepared rapid gradient echo (repetition time = 2400 ms, echo time = 2.06 ms, 230 mm field of view, matrix size 256 × 256, 224 sagittal slices, 0.9 mm^3 voxel size).

rs-fMRI Data Preprocessing

rs-fMRI data were preprocessed using the Functional Connectivity (CONN) toolbox (http://web.mit.edu/swg/software.htm) following the standard CONN preprocessing pipeline (55): functional realignment and unwarp (56), slice-timing correction (57), outlier identification (volumes exceeding >0.9 mm framewise displacement or global blood oxygen level–dependent signal changes above 5 SD), direct segmentation and normalization [images were normalized into standard Montreal Neurological Institute space and segmented into gray matter, white matter, and cerebral spinal fluid tissue classes using SPM12 unified segmentation and normalization procedure (58)], and functional smoothing (images were smoothed using spatial convolution with a Gaussian kernel of 8 mm full width at half maximum). After preprocessing, we applied CONN's default denoising pipeline composed of linear regression of confounding effects and temporal bandpass filtering. White matter and cerebral spinal fluid noise were estimated and regressed out using an anatomical component-based noise correction procedure (59). To reduce motion artifacts, we included 12 noise parameters as nuisance regressors (3 translation and 3 rotation parameters and their associated first-order derivatives) at the single-subject level. Temporal frequencies were filtered to 0.01 to ~0.09 Hz to focus on low-frequency fluctuations while minimizing the influence of physiological, head motion, and other noise sources. These noise and motion confounders were regressed out in the lower-level multiple regression analyses for each participant before any group-level analyses were carried out.

Seed-Based Correlation Analyses

Seed-based analyses were performed using the CONN toolbox by computing the temporal correlation between the blood oxygen level–dependent signals from regions of interest to all other voxels in the brain. Based on previous pilot results by our group (43), we selected 7 seeds from the probabilistic Harvard-Oxford Subcortical Structural Atlas (60): left and right putamen, left and right caudate, left and right pallidum, and bilateral middle frontal gyrus. Group-level analyses were performed using the general linear model implemented in the CONN toolbox with natural log-transformed Mn concentrations at each time point as predictors and iFC as the outcome. Given that Mn concentrations were moderately correlated across 2 of the 3 time points (r values = 0.03–0.42), we performed separate analyses for each of the 3 time points. To investigate the moderating effect of sex on the associations between dentine Mn and iFC, we examined interactions between sex and Mn adjusting for age and SES. Statistical images were thresholded using a cluster-corrected threshold of p < .05 false discovery rate correction (44,61–63). To control for the number of comparisons (n = 21; 7 seed regions × 3 Mn time points), we applied a secondary false discovery rate correction and only report findings surviving both false discovery rate corrections. Finally, in a sensitivity analysis, we investigated sex-stratified associations between dentine Mn and iFC in regions found to have a significant interaction term. Stratified models were implemented in R (version 3.5.1) with the glm package.

RESULTS

Descriptive Statistics

Participant demographics are presented in Table 1. Among the 71 participants (38 [54%] female), the mean age of participants

Table 1. Sex-Stratified Sociodemographic Characteristics of 71 Adolescents From Northern Italy

Sociodemographic Characteristics	Female, *n* = 38	Male, *n* = 33	Total, *N* = 71
Age, Years			
Mean (SD)	19.7 (2.08)	19.1 (2.36)	19.4 (2.22)
Median [min, max]	19.7 [15.9, 23.1]	19.1 [15.9, 23.4]	19.4 [15.9, 23.4]
IQ			
Mean (SD)	103 (10.7)	106 (9.25)	104 (10.1)
Median [min, max]	105 [78, 117]	105 [77, 121]	105 [77, 121]
SES, *n* (%)			
Low	5 (13.2%)	2 (6.1%)	7 (9.9%)
Medium	25 (65.8%)	23 (69.7%)	48 (67.6%)
High	8 (21.1%)	8 (24.2%)	16 (22.5%)
Site, *n* (%)			
BM	13 (34.2%)	18 (54.5%)	31 (43.7%)
GL	13 (34.2%)	6 (18.2%)	19 (26.8%)
VC	12 (31.6%)	9 (27.3%)	21 (29.6%)
Prenatal Mn			
Mean (SD)	0.433 (0.165)	0.471 (0.192)	0.451 (0.178)
Median [min, max]	0.417 [0.168, 1.14]	0.470 [0.148, 0.869]	0.427 [0.148, 1.14]
Postnatal Mn			
Mean (SD)	0.137 (0.0477)	0.119 (0.0555)	0.129 (0.0519)
Median [min, max]	0.125 [0.0486, 0.256]	0.121 [0, 0.238]	0.124 [0, 0.256]
Childhood Mn			
Mean (SD)	0.000821 (0.000422)	0.000818 (0.000447)	0.000820 (0.000431)
Median [min, max]	0.000720 [0.000328, 0.00267]	0.000757 [0, 0.00208]	0.000727 [0, 0.00267]

IQ was measured using the Wechsler Intelligence Scale for Children, 3rd edition (47). Sociodemographic characteristics did not differ between males and females ($p > .05$).

BM, Bagnolo Mella; GL, Garde Lake; max, maximum; min, minimum; Mn, manganese; SES, socioeconomic status; VC, Valcamonica.

was 19.4 years (SD = 2.2 years). The average IQ score of participants was 104 (SD = 10.1). The majority of participants were from families reporting medium SES (66%). Dentine Mn was log-transformed to reduce skewness and approximate a normal distribution. There were no statistically significant differences found in dentine Mn, age at scan, IQ, and SES between male and female participants. Dentine Mn concentrations in each time point, stratified by sex, are presented in Figure 1.

Seed-Based Correlation Analyses of Sex-Specific Associations

For all time points, the seed-based correlation analyses revealed sex-specific associations between dentine Mn and iFC (Table 2, Figure 2). Seed-to-region connectivity and peak coordinates in Montreal Neurological Institute space for models showing significant interactions between dentine Mn and sex are reported in Table 2. We observed sex-specific associations between prenatal dentine Mn and iFC in the following connections: 1) left caudate and left occipital pole, 2) left putamen and left middle frontal gyrus, 3) left putamen and left occipital fusiform gyrus, and 4) middle frontal gyrus and right occipital pole. Sex-stratified analyses showed that in connections 1 and 3, prenatal Mn exposure was associated with increased iFC in females and decreased iFC in males, whereas connections 2 and 4 show an inverse pattern (Table S1). Mn uptake during the early postnatal period (<1 year of age) showed sex-specific effects on iFC between the right putamen and the right cerebellum, with decreased iFC in females and increased iFC in males. Exposure to Mn during the early childhood period (1 to ~6 years) showed sex-specific effects on iFC between 1) the left putamen and the right superior division of the lateral occipital cortex and 2) the middle frontal gyrus and the left posterior division of the middle temporal gyrus. In both connections, increased Mn exposure was associated with increased iFC in females and decreased iFC in males.

DISCUSSION

In this study, we sought to test our Developmental Origins of Health and Disease–based hypothesis that Mn uptake during early-life CWs of development is associated with changes in functional connectivity in adolescence, and that environmentally associated brain changes are sex specific. Using an objective, retrospective biomarker of Mn uptake during prenatal, early postnatal, and childhood periods and rs-fMRI in adolescence, we found significant sex-specific associations between dentine Mn at all time points and iFC in adolescents. Moreover, we report associations in different networks depending on the timing of exposure, suggesting that different brain networks may present distinctive CWs of vulnerability to Mn. During the prenatal period, we observed sex-specific associations between dentine Mn and functional connectivity between the dorsal striatum (caudate and putamen) and regions in the occipital and frontal lobes and between the middle frontal gyrus and the occipital lobe. During the early postnatal

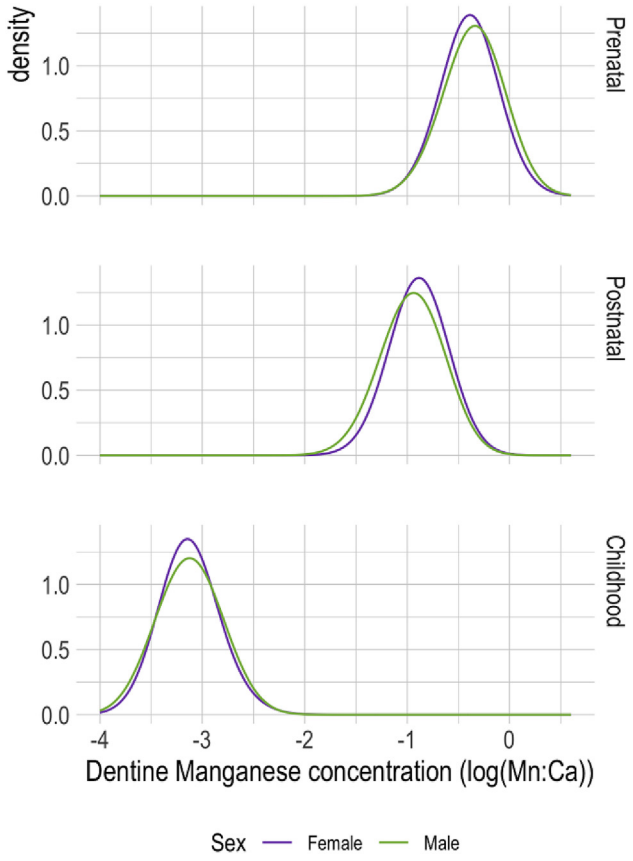

Figure 1. Prenatal, postnatal, and early childhood manganese (Mn) concentrations (log) measured in naturally shed deciduous teeth of 71 study participants by sex. The density curve represents the relative frequency of all observations, such that the area underneath it is exactly 1. Dentine Mn did not differ between males and females (logistic regression adjusted for socioeconomic status and age, $p > .05$). Ca, calcium.

period (<1 year), dentine Mn was associated with sex-specific changes in the right putamen and the cerebellum. Finally, during the early childhood period (1 to ~6 years), exposure to Mn showed sex-specific effects on iFC between the putamen and the occipital lobe and between the frontal and temporal lobes. Our results highlight that the effect of Mn on iFC differs in magnitude and directionality between females and males. Four connections showed increased iFC in females and decrease in males, whereas 3 connections showed a reverse pattern. These sex-specific effects may not be attributed to sex differences in exposure or absorption of Mn, because we report similar Mn uptake levels between males and females. Despite the proximity of study participants to active ferroalloy smelting activity, dentine Mn levels measured in this study are comparable to previously reported levels in other populations and are not suggestive of exceptionally heightened exposure (28,43,64,65). This study contributes to the growing literature suggesting that early-life Mn uptake impacts neurodevelopmental outcomes by providing mechanistic insights into the brain regions underlying these associations. Using our dentine biomarker to provide a retrospective marker of Mn uptake in 3 developmental stages, we identified 3 CWs of vulnerability to this neuroactive metal. Finally, our findings of sex-specific associations support our hypothesis that the effect of early-life exposure to Mn differs by sex.

MRI allows in vivo visualization of the brain. It is noninvasive and free of ionizing radiation, making it suitable for research in children. In the field of environmental epidemiology, MRI plays a critical role in elucidating biological mechanisms underlying Mn neurotoxicity. Until recently, the use of brain imaging in environmental health studies of Mn neurotoxicity has focused on structural brain abnormalities, primarily in the basal ganglia, and mostly targeted highly exposed workers (66,67). Numerous structural basal ganglia abnormalities have been reported in workers exposed to Mn, including T1 hyperintensities (68–71), lower apparent diffusion coefficient (68), higher pallidal index (72,73), and lower fractional anisotropy (74–76). Only 2 occupational MRI studies have investigated functional brain changes related to Mn exposure (77,78). Chang *et al.* (77) showed Mn-induced alterations in brain activity during a working memory task, with higher activation in the basal ganglia (i.e., including the putamen) in exposed welders. Seo *et al.* (78) showed decreased activation of the frontal, parietal, and insular cortices in welders during an executive function task. Our findings are consistent with prior structural and functional MRI studies, because we detect effects in the caudate and putamen, which are central components of the basal ganglia. This study builds on the previous literature by adding 1) a focus on lower nonoccupational exposures in children, 2) longitudinal retrospective measures of

Table 2. Results From Seed-Based Correlation Analysis Demonstrating Significant Sex-Specific Associations Between Dentine Mn at Three Time Points and Intrinsic Functional Connectivity in Adolescents

Exposure Time Point	Seed-to-Region Connectivity	Cluster (x, y, z)	Cluster Size	β	*p*-FDR
Prenatal	Left caudate—left occipital pole	(−04, −90, +08)	223	0.67	<.001
	Left putamen—left middle frontal gyrus	(−30, +26, +42)	64	−0.71	.014
	Left putamen—left occipital fusiform gyrus	(−28, −78, −16)	60	0.67	.014
	Middle frontal gyrus—right occipital pole	(+14, −98, +12)	99	−0.92	.003
Postnatal	Right putamen—right cerebellum	(+42, −68, −54)	74	−0.70	.009
Early Childhood	Left putamen—lateral occipital cortex, right superior division	(+12, −52, +58)	90	0.64	.003
	Middle frontal gyrus—middle temporal gyrus, left posterior division	(−50, −22, −04)	138	0.74	.002

All models controlled for age (years) and SES. Voxel threshold $p < .001$ (uncorrected); cluster threshold $p < .05$ (*p*-FDR corrected). Coordinates presented are in MNI space. All coefficients refer to sex-Mn interaction term.

FDR, false discovery rate; Mn, manganese; MNI, Montreal Neurological Institute; SES, socioeconomic status.

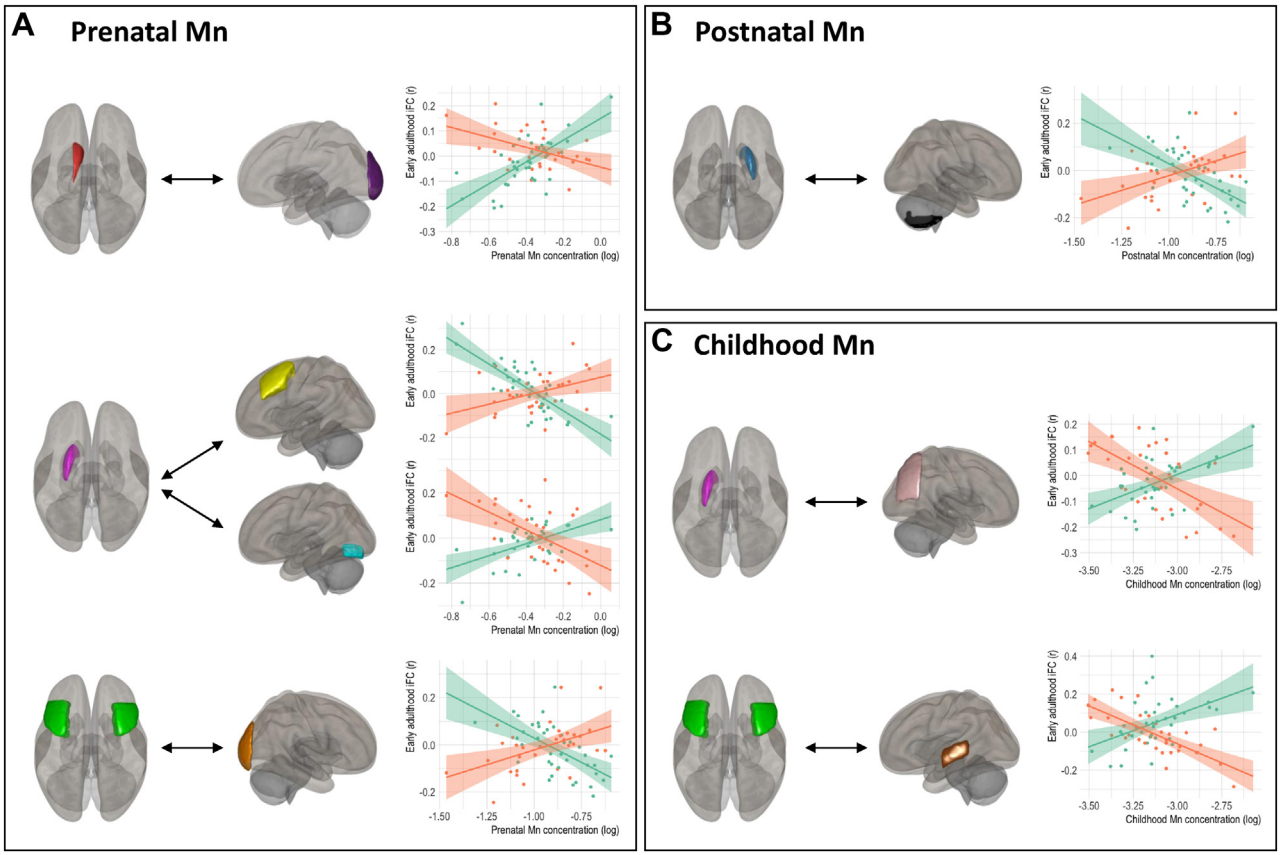

Figure 2. Sex-specific correlations between intrinsic functional connectivity (iFC) in adolescents and natural log-transformed dentine manganese (Mn) from 3 time points: **(A)** prenatal, **(B)** postnatal, and **(C)** childhood ($N = 71$). Brain regions are color-coded: left caudate, red; right putamen, blue; left putamen, pink; middle frontal gyrus, green; left occipital pole, purple; left middle frontal gyrus left, yellow; left occipital fusiform gyrus, teal; right occipital pole, orange; cerebellum, black; lateral occipital cortex, light pink; middle temporal gyrus, brown. Graphs plot regression lines and standard errors for females (green) and males (orange). Only significant interactions ($p < .05$) between dentine Mn and sex are shown. Regions are color-coded for visualization purposes. Exact cluster locations in Montreal Neurological Institute coordinates and cluster sizes are reported in Table 2.

Mn uptake allowing the detection CWs of susceptibility, 3) direct and objective measurement of Mn concentrations instead of self-reported exposure history, and 4) analyses of sex-specific effects.

Substantial research demonstrates associations between early-life Mn exposure and adverse neurodevelopmental outcomes (9,28,79,80). In a recent pilot study, de Water *et al.* (43) reported associations between postnatal Mn dentine concentrations and iFC in areas of the brain implicated in cognitive control and motor function. In this study, we built on this pilot work to explore sex-specific vulnerabilities to the effect of early-life Mn exposure on iFC. Our findings indicate that Mn exposure is differently associated with functional connectivity in males and females in brain regions involved in cognitive control and motor function. Mn concentrations were associated with sex-specific effects on iFC between regions of the basal ganglia (striatum or caudate–putamen) and cortical regions (occipital and frontal).

The cortical–subcortical connections impacted by Mn exposure in our study are known to be associated with neurologic health outcomes in adults. According to the current model of basal ganglia function in adults, the striatum is the main entry point of cortical information to the basal ganglia; it receives afferents from widespread areas of the cerebral cortex through the thalamus (i.e., corticobasal ganglia–thalamocortical loops) (81,82). These circuits are crucial for emotional, cognitive, and motor functions (83–87). The caudate and putamen are involved in the planning and execution of movement, learning, memory, and reward (88–90). Mn dyshomeostasis may disrupt the corticobasal ganglia circuitry, because Mn is known to accumulate in basal ganglia structures (42,91). Increased caudate connectivity (92), putamen dysfunction (93), and increased putamen–cerebellum connectivity (94) have been observed among adults diagnosed with Parkinsonism. Mn-exposed occupational workers demonstrate clinical symptoms mirroring Parkinson disease (95). Middle frontal gyrus and middle temporal gyrus connectivity have also been associated with cognitive and executive function, specifically literacy and numeracy abilities (96,97), with increased connectivity in the middle frontal gyrus within the occipital pole network reported among children with autism spectrum disorder (98). Little is known about the dynamic

development of these circuits during childhood. Given the known vulnerability of these circuits to perturbation during development, our study adds to the literature by relating Mn exposure to alterations in typical neurodevelopment of subcortical–cortical connections.

Our novel approach combining neuroimaging in late adolescence with the use of deciduous teeth as a retrospective biomarker of early-life Mn uptake allows us to test our Developmental Origins of Health and Disease–based hypothesis. Traditional biomarkers of Mn exposure (e.g., urine, blood, hair) used in prior studies are unable to directly measure exposure in fetal life. Further, traditional biomarkers fail to provide longitudinal exposure spanning several potential CWs of development including the fetal, postnatal, and childhood periods. There is a lack of consensus regarding the appropriate biomarker to assess Mn-associated impacts on the developing brain because each biomarker reflects differences in pharmacokinetics, and therefore, associated health effects may be matrix dependent. Instead, dentine Mn is a validated biomarker providing a direct measure of Mn across prenatal and postnatal periods, which enabled us to detect CWs for effects of Mn exposure on iFC of the brain. Results from a recent study in the same cohort, using the dentine biomarker to study associations between Mn and neurocognition, suggest a subtle shift over time from a beneficial role of Mn during the prenatal period to a more detrimental role in childhood (41). Our unique study design is able to provide detailed insights into the neural mechanisms that may underpin these associations between early-life Mn exposure and cognitive and motor control reported in prior studies (26,28,32,41,99).

Very few previous investigations have explored sex-specific effects of early-life Mn on neurodevelopmental outcomes, and although most of them detect a difference in vulnerabilities by sex, the direction of reported associations is inconsistent. Early-life Mn has been positively associated with improved cognition and motor outcomes among females compared with males (26,100). Contrastingly, other groups have found a negative association between Mn concentrations and nonverbal performance, motor outcomes, visuospatial learning, and IQ scores among females (28,32,79,99). Discrepancies in direction of association may be due to differences in the task used to assess behavior, type of biomarker used to assess exposure, and timing of exposure and/or outcome assessment. Our results are in line with previous studies, suggesting that male and female neurodevelopment is not equally vulnerable to the effect of Mn exposure, and the direction of effect varies not only in magnitude but also in direction. Notably, unlike assessments of cognition and motor function, interpretation of directional changes in iFC is challenging. Increased functional connectivity does not necessarily indicate better performance, as it has been associated with memory and cognitive impairments (101,102), anxiety (103), and epilepsy (104), or may reflect a compensatory mechanism. Despite this limitation, our results add to the growing literature relating early-life Mn exposure with alterations in typical neurodevelopment and suggest that males and females are not equally vulnerable to Mn exposure, with effects persistent throughout extended adolescence.

To our knowledge, this is the first study to use a neuroimaging approach to examine sex-specific effects of early-life Mn exposure on neurodevelopmental outcomes in adolescence. We acknowledge several limitations to our research. The modest sample size of this study limits the generalization of our findings. Exclusion criteria such as diagnosis of neurologic or psychiatric disorders could potentially exclude participants with the highest levels of Mn exposure. The exact age at which teeth were shed was not documented in this study. However, because the age of shedding is not expected to be related to MRI data, any resulting bias would likely be toward the null. Pubertal stage data were not collected, which could potentially be considered as a covariate. Moreover, because the interpretation of the directionality of our observed associations is challenging, future studies with a larger sample size should include cognitive and motor outcomes to test whether Mn-associated changes in iFC are associated with increased or decreased performance. Finally, children and adolescents are rarely exposed to Mn alone and, in most cases, are exposed to low levels of several metals simultaneously. Coexposure to multiple metals may influence Mn toxicity (105,106). Thus, future studies should explore associations between early-life exposure to mixtures of metals and iFC later in life.

In conclusion, we identified sex-specific CWs of susceptibility to Mn exposure on iFC in areas of the brain implicated in cognitive and motor function. These findings suggest that the developing brain is especially vulnerable to Mn exposure, with effects lasting at least through late adolescence and possibly later. More research into identifying CWs of development that are sensitive to environmental insults will improve public health and risk management and may help identify especially susceptible subgroups for interventions and methods to optimize Mn exposure. Future research is needed to link sex-specific neural correlates with their behavioral and cognitive outcomes.

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ARTICLE INFORMATION

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